

Editorial

IOTA (International Ovarian Tumour Analysis): Celebrating 20 years of multidisciplinary research

This issue of Facts, Views and Vision in ObGyn is almost entirely dedicated to the second International Ovarian Tumour Analysis (IOTA) congress (17-18 April 2015, Leuven, Belgium).

IOTA is an example of what can be achieved when there is good communication between different disciplines and selfless collaboration between departments both nationally and internationally. While preparing my PhD thesis in 1995 I attended the ESEGO congress in Gothenburg where I was most impressed by innovative lectures on ovarian tumour diagnosis and colour Doppler ultrasonography by Tom Bourne, now professor at Imperial College London, and Lil Valentin, professor in Malmö, Sweden. In the same year a lecture on Artificial Neural Networks given by Joos Vandewalle, professor in Electrical Engineering at KU Leuven was another stepping-stone of later research. These networks were trained by feeding them with examples and could solve difficult diagnostic problems and also make predictions. After his lecture I discussed with Prof Vandewalle potential applications in medicine. The next day we had a meeting in his office together with Sabine Van Huffel and Bart De Moor. This was the start of a long and very fruitful collaboration between medical specialists and civil engineers from the department of Electrical Engineering.

After we found a common language to communicate with each other we started developing logistic regression models and artificial neural networks to predict whether an ovarian tumour was malignant or benign based on clinical study data collected at UZ Leuven (Timmerman et al., 1999). Given this fantastic opportunity, several collaborations developed. Herman Verrelst was my running mate. Since that time he has started up four spin off companies and is currently CEO of Cartagena. I felt very grateful that Tom Bourne, who had written several seminal research papers in the area, agreed to visit our hospital and give a lecture in Leuven. This new collaboration was very inspirational. Our first research papers were guided and critically reviewed by William Collins, then professor at Kings College London. His scientific rigour, absolute commitment to sound methodology and attention to every detail formed a solid base for all subsequent research by the group. At my PhD defence in December 1997, I felt very privileged that Ignace Vergote, professor in Gynaecological Oncology, and Kamiel Vandenberghe, professor in Obstetric Ultrasound, were my promoters, and that Stuart Campbell, professor at Kings College London and founder of ISUOG (International Society of Ultrasound in Obstetrics and Gynaecology) and the journal 'Ultrasound in Obstetrics and Gynaecology', was external member of the jury. Instead of this PhD defence signalling the end of a period of research, it was in fact only the beginning.

In 1998 I discussed starting the IOTA group together with Tom Bourne. We had several meetings with Lil Valentin to discuss terms, definitions and measurements to describe ovarian tumours (Timmerman et al., 2000). During a meeting in the gardens of the Old Beguinage in Leuven, Tom and I started the IOTA group together with Lil Valentin, William Collins, Herman Verrelst, Sabine Van Huffel and Ignace Vergote. In 2000 we co-organized a large international congress in Leuven 'A Journey from Gamete to Newborn' driven by the enthusiasm of Willem Ombelet, editor-in chief of this journal, Jan Deprest, and Annie Vereecken. While planning this congress Willem Ombelet and Koen Vanmechelen had the innovative idea of creating a journal with a unique combination of interviews, medical information and art. In keeping with this theme, invited speakers at the congress were each given a glass sculpture of a chicken created by Koen Vanmechelen, which is now a priceless collectors' item.

The 2000 congress was the first large meeting of all the IOTA investigators and it provoked animated discussions and instilled enthusiasm in the group. Lil Valentin introduced Antonia Testa, now consultant in gynaecology at Sacro Cuore Rome, who joined the Steering Committee and who encouraged her own research group and numerous other Italian colleagues and centres to become active members of IOTA. Subsequently many innovative models were developed and tested together with the research groups of Sabine Van Huffel and Bart De Moor. These models supported medical decisions and led to 12 successful PhD defences both in the Group of Biomedical Sciences and in the Group of Sciences at KU Leuven. Later this methodology was

disseminated to other medical areas (e.g. neonatology, endocrinology, intensive care medicine, genetics and oncology). After their doctoral degree a number of these researchers were appointed at KU Leuven, Ghent University, Vlaams Instituut voor Biotechnologie (VIB), Institut Bordet Brussels, Stanford University, Broad Institute MIT and Harvard University of California, San Francisco and Genentech. After his PhD defence Ben Van Calster joined the IOTA Steering Committee and now supervises the methodology and biostatistics for the study. More recently Arnaud Installé defended his PhD having developed the ‘Clinical Data Miner’, and he is also staying with the project. Many clinicians have also made a major contribution. Even after defending her PhD thesis Dr Caroline Van Holsbeke remains a pivotal part of the IOTA team, despite doing so alongside having a full-time commitment at the ZOL hospital in Genk (Van Holsbeke et al., 2009; Timmerman et al., 2010; Van Calster et al., 2014; Testa et al., 2014). At Imperial College in London, Ahmad Sayasneh and colleagues completed a thesis on IOTA phase 4, showing that the IOTA models and rules work in the hands of operators with varying experience and training. Around this time, Jeroen Kaijser took over the running of IOTA phase 5. Jeroen will defend his PhD on the eve of the second IOTA Congress. In February 2014 Antonia Testa organized the national ultrasound course in Rome, where over 700 Italian gynaecologists passed the IOTA MCQ test.

Today there are more than 40 international centres contributing to the IOTA group, all committed to improving the classification of ovarian tumours. The group includes gynaecologists, radiologists, clinical biologists, oncologists, civil engineers, biostatisticians, mathematicians and psychologists. The close relationships formed within IOTA have led to many other collaborations between members of the IOTA group outside the core project. An example of this was seen in 2007 when Thierry Van den Bosch defended his PhD thesis and together with Francesco Leone, consultant gynaecologist in Milan, we founded the IETA group (International Endometrial Tumour Collaboration), which is now the largest collaborative imaging study on endometrial and uterine pathology.

No study can afford to stand still. Phase 5 of the IOTA study will be analysed soon and this will give important insights into the long-term behaviour of ovarian masses and answer whether IOTA models and rules work in masses selected for expectant management. We recognize that other imaging modalities have a role to play and in the future the IOTA-MRI project will address the issue of how MRI can best fit into protocols for the assessment of ovarian tumours. Even before the IOTA study started many people said that a biomarker would soon be discovered that would render imaging redundant. Twenty years later and this has not happened. The IOTA group assessed the performance of available markers (CA 125, HE4, OVX1 and ROMA) and found none compared to the performance of ultrasound. However it is important to keep looking for new markers and this has been the motivation behind developing the “translational” IOTA arm of the project.

It is impossible to thank by name the many people who have contributed to the IOTA studies, as there are literally hundreds. However it is a team effort and nothing could be done without the commitment, trust and integrity of everyone involved. It gives me immense pleasure to be able to thank all these fantastic colleagues and to celebrate together 20 years of multidisciplinary collaboration.

References

- Testa A, Kaijser J, Wynants L et al. Strategies to diagnose ovarian cancer: new evidence from phase 3 of the multicentre international IOTA study. *Br J Cancer*. 2014;111:680-8.
- Timmerman D, Verrelst H, Bourne TH et al. Artificial neural network models for the preoperative discrimination between malignant and benign adnexal masses. *Ultrasound Obstet Gynecol*. 1999;13:17-25.
- Timmerman D, Valentin L, Bourne TH et al. Terms, definitions and measurements to describe the sonographic features of adnexal tumors: a consensus opinion from the International Ovarian Tumor Analysis (IOTA) Group. *Ultrasound Obstet Gynecol*. 2000;16:500-5.
- Timmerman D, Ameje L, Fischerova D et al. Simple ultrasound rules to distinguish between benign and malignant adnexal masses before surgery: prospective validation by IOTA group. *BMJ*. 2010;341:c6839.
- Van Calster B, Van Hoorde K, Valentin L et al. International Ovarian Tumour Analysis Group. Evaluating the risk of ovarian cancer before surgery using the ADNEX model to differentiate between benign, borderline, early and advanced stage invasive, and secondary metastatic tumours: prospective multicentre diagnostic study. *BMJ* 2014;349:g5920.
- Van Holsbeke C, Van Calster B, Testa AC et al. Prospective internal validation of mathematical models to predict malignancy in adnexal masses: results from the international ovarian tumor analysis study. *Clin Cancer Res*. 2009;15:684-91.

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